

Will MR image-guided brachytherapy be a standard of care for cervical cancer in future? An Indian perspective

Cancer of the uterine cervix is the leading cancer among the female population in India. Radical external chemoradiotherapy and brachytherapy is the treatment of choice for locally advanced cervical cancers. Brachytherapy plays a pivotal role for its ability to deliver very high dose to the tumor while reducing the dose to the surrounding critical organs. In the last decade, external beam radiotherapy (EBRT) has seen technological advances in terms of intensity modulated radiotherapy (IMRT), image guided radiotherapy (IGRT), etc. However, the advances in brachytherapy for cervical cancers are not as rapid as EBRT, which have shown significant potential to improve local control rates and reduce toxicities.

In earlier days, there were systems like Manchester, Paris, Stockholm derived from rich clinical experience to deliver specified dose to the tumor fairly accurately even in the absence of treatment planning systems. Later, with the development of various after-loaded applicators and different radium substitutes like Cs-137, Co-60, Ir-192, the potential of brachytherapy became evident and it has become an integral part of radical radiotherapy. High Dose Rate (HDR) remote after-loading coupled with advances in treatment planning systems has ensured well-defined protocols and methods for brachytherapy dose analysis. However, the imaging modality used in brachytherapy was largely limited to 2D orthogonal radiographs. The major limitation of the conventional imaging modalities is that they are applicator and point based and there is a lack of information on the tumor volumes and organs at risk (OARs). Conventionally, point doses are calculated for rectum and bladder according to ICRU 38 recommendations. But point doses do not represent the dose received by the entire volume of the organs, due to which the doses to the OARs are not accurately known. Hence, there is no significant correlation between the point doses and incidence of toxicities, especially in bladder. In addition, tumor cannot be seen in the radiographs, hence local control of the

disease also is a challenge especially in larger tumors. In the last two decades, significant technological advances have resulted in the use of newer imaging modalities, planning algorithms, and treatment delivery techniques. This has resulted in the use of imaging techniques for 3D data acquisition, contouring for both target and various organs and to optimize treatment planning for brachytherapy applications.

Various imaging modalities like ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scans have been explored. Among all the imaging modalities, MRI is becoming increasingly popular for the diagnosis and treatment planning for EBRT and brachytherapy. Image-guided brachytherapy (IGBT) has been mainly possible due to MRI, where it is possible to image the applicator with tumor volume and other normal tissues. MR-based IGBT is practiced mainly in Europe and a few centers in the US. As compared to robust 2D outcome data, it is still evolving with initial clinical data showing promising results. Like any other advanced technique, viz. IMRT, IGRT in external beam radiation therapy, IGBT too requires stringent quality assurance procedures to be adhered to; otherwise, it will lead to a geographical miss and even increased toxicities to patients. American Brachytherapy Society (ABS) Image-guided Brachytherapy Working Group (IGBWG) has provided guidelines in reporting the image-based brachytherapy, which recommends the prescription of dose to a volume rather than a point. Later, Groupe Européen de Curiethérapie (GEC) working group of European Society of Therapeutic Radiation Oncology (ESTRO) published guidelines for the practice and reporting of image-based brachytherapy, which have been widely accepted so that a unified approach is formed among the users of image-based brachytherapy.^[1]

One of the largest series published so far is from Vienna group, who have reported the clinical outcome of 156 patients treated with image-guided adaptive brachytherapy combined with 3D conformal EBRT, with and without chemotherapy.^[2] The results are promising with excellent local control rates of 95–100% at 3 years in limited/favorable (IB/IIB) and 85–90% in large/poor response (IIB/III/IV) groups, with acceptable treatment-related morbidity rates. Compared to their historical series, there is relative

Access this article online	
Quick Response Code: 	Website: www.jmp.org.in
	DOI: 10.4103/0971-6203.92713

reduction in pelvic recurrence by 65–70% and reduction in major morbidity. Similar outcome data published from Paris and Mumbai endorse this.^[3] This is being tested further in an ongoing multicentric study involving several institutes in Europe, USA, and Asia (EMBRACE study).

Although IGBT in principle appears promising, it needs critical review and introspection for applicability and adaptation in our setting, especially in high patient number centers and developing countries.

It is estimated that 80% of the new cervical cancer cases occur in developing countries like India, which reports approximately one-fourth of the world's cases of cervical cancer each year. Moreover, two-thirds of the cancers are diagnosed with advanced stages which, coupled with absence of better equipment, imaging infrastructure, and trained personnel in majority of centers, makes the management challenging. Therefore, in addition to an aggressive screening program for early detection, we also need to make optimum use of resources such that better outcome in terms of disease control and toxicities is obtained. Hence, in order to apply international guidelines and recommendations to our setting, these aspects need to be discussed.

In the recent times, conventional simulators are gradually being replaced with CT simulators, and hence the use of CT images is increasing for brachytherapy planning. It is well documented that CT images provide better soft tissue resolution and the doses to OARs could be accurately determined as compared to conventional orthogonal films in intracavitary cervix brachytherapy. Although MRI is superior to CT for imaging and identifying cervical cancer extension, many institutions do not have access to an MRI. Studies have revealed that both CT and MRI modalities are adequate for OAR analysis.^[4] However, CT tumor contours can significantly overestimate the tumor width, resulting in significant differences to High Risk Clinical Target Volume (HR-CTV) dose compared with that using MRI. Hence, MRI remains the standard for HR-CTV definition.^[1]

A survey conducted regarding the pattern of practice of intracavitary brachytherapy in USA revealed that BT planning by X-ray films is used by 24% centers.^[5] CT is the most commonly used imaging modality in 57% centers, while MRI is used by less than 20% centers only. Before 1990s, orthogonal X-ray film simulation was the standard method. After the integration of CT into radiation oncology departments, use of 3D imaging has increased and now represents the standard for brachytherapy planning. In a similar survey conducted in Australia and New Zealand, it was found that 65% centers use 3D CT imaging, while 30% use X-rays. 20% use a combination of imaging modalities including CT, ultrasound, and MRI.^[6] Only 20% centers follow GEC ESTRO recommendations for contouring,

prescribing dose, and reporting treatment. Similar survey conducted in Europe reveals that CT imaging increased to 61% in 2010 as compared to 33% in 2002.^[7]

Unfortunately, though India has the highest burden of cervical cancers as stated earlier, such a survey does not exist and we do not have the data regarding patterns of care of brachytherapy and its related details. We need centers with sufficient resources and possibly professional bodies to take up such surveys, and based on the outcome, we need to formulate national guidelines taking into account the international recommendations. Research is also required in low-cost imaging modalities such as ultrasound,^[8] so that developing countries can evaluate and adopt the benefits of IGBT.

Conventionally, stainless steel applicators were made, which were robust, sturdy, and economical. However CT imaging produces artifacts that do not allow the OARs to be visualized clearly. The inability to obtain MRI scans with the conventional, stainless steel after-loading applicators has discouraged the implementation of MRI for gynecologic brachytherapy treatment planning to a large extent. New applicators made from polymer material and titanium were introduced. These applicators are fragile and expensive and generally not affordable by all centers. In addition, titanium produces susceptibility artifacts and image distortion with MRI. Moreover, it also produces heating effects when imaged with higher magnetic field (3 T). Such concepts have to be clearly understood and mandate further research in applicator development. Systematic investigation as a part of commissioning is required when new applicators are procured to be used with MRI/CT modalities. With conventional applicators, radiopaque dummies to represent source channel / positions were provided by the vendors; however, CT / MR compatible applicators lack dummies, adding to uncertainties during reconstruction of the applicator that may have consequences in dose distribution. Many methods like use of 6 F catheters filled with water, iodine, oil, etc., have been used to overcome these limitations. Further research is required to produce these applicators indigenously in our country, which may benefit the centers that cannot afford such expensive applicators.

Contouring and target volume delineation with the use of CT imaging for external beam radiation therapy has been in routine practice and is a success story now. However, contouring target volumes and OARs for brachytherapy planning is a new concept and with applicators *in situ* adds to the challenge. CT image based contouring of OARs is being practiced mainly to determine the dose to OARs. Contouring for cervix cancer, especially delineation of Gross Tumor Volume, HR-CTV and Intermediate Risk (IR)-CTV with the use of MRI, was first introduced by GEC ESTRO in 2005. This is associated with some learning curve and

definitely needs training, especially in MR anatomy and pathology, including gray zones.

From the physicist's point of view, there are new concepts in reconstruction, prescription, and optimization. GEC ESTRO has published guidelines for reconstruction, which need to be adapted for a successful implementation of IGBT program.^[9] The planning and optimization is HR-CTV based and not point A based which has been practiced for decades. The transition from point A based to HR-CTV based optimization has been a big challenge. Hence, the change in the standard loading pattern (pear shape) as compared to the historical dosimetry systems is still being addressed and investigated.^[10] In addition, there is a lot of debate in the literature about the use of inverse planning for cervical cancer brachytherapy.^[11]

MR image based brachytherapy in cervical cancer is evolving with promising results. It definitely needs an upgradation in the existing infrastructure or additional enhanced set-up in terms of imaging, hardware and software, and training of staff.

In developing countries including India, where locally advanced cervical cancer is a major problem, appropriate, adequate, and quality treatment to all patients is the key to success. In India, there has been a rapid rise of corporate healthcare and a steady improvement in radiation facilities in the government sectors. Most of the facilities have CT scanners / simulators for RT planning. An attempt should be made by all high-volume centers to incorporate some form of image-based approach for both teletherapy and brachytherapy for cervical cancers. Although published data on 3D image-based brachytherapy in cervical cancers from India are sparse, they do not preclude its use. There is an urgent need to generate robust data on CT or MR 3D image based brachytherapy planning and suitable evidence through clinical studies to resolve the issues further in optimizing treatment for cervical cancers.

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How to cite this article: Deshpande DD. Will MR image-guided brachytherapy be a standard of care for cervical cancer in future? An Indian perspective. *J Med Phys* 2012;37:1-3.

Source of Support: Nil, **Conflict of Interest:** None declared.